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FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
01/07/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/583,795	NAKANO ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,6-8,14-16,19-22,24-27,29,31,32 and 34-46* is/are pending in the application.

4a) Of the above claim(s) *19,20,24-27 and 43-46* is/are withdrawn from consideration.

5)☒ Claim(s) *3,6,7,21,22,29 and 39* is/are allowed.

6)☒ Claim(s) *8, 14-16, 31, 32, 34, 35-38, and 40-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 September 2008* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/11/08 and 9/29/08* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 3, 6-8, 14-16, 19-22, 24-27, 29, 31, 32 and 34-46 are all the pending claims for this application.

2. Claims 1, 2, 4, 5, 9-13, 17, 18, 23, 28, 30 and 33 were cancelled, Claims 3, 6-8, 14-16, 21, 22, 29, 31 and 32 were amended and new Claims 34-46 were added in the Response of 9/29/08.

3. Claims 19, 20 and 24-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) in the reply filed on 1/18/08.

Newly submitted claims 43-46 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The elected claims are drawn to an anti-glypican 3 antibody and new Claims 43-46 are drawn to a method of treatment.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 43-46 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

4. Claims 3, 6-8, 14-16, 21, 22, 29, 31, 32 and 34-42 are all the pending claims under examination.

5. Applicants amendments to the claims have necessitated new grounds for rejection.

Priority

6. The copy of the certified translation for Japanese language priority document, JP 2004-2-3637, with a filing date of 7/9/04, and filed with the Response of 9/29/08 is acknowledged.

Information Disclosure Statement

7. The IDS' of 4/11/08 and 9/29/08 have been considered and entered. Each IDS lists the same reference. The information is cumulative under 37 CFR 1.56(b), therefore the reference on the 1449 form from the IDS of 9/29/08 has been stricken. An initialed and signed copy of the 1449 forms from each IDS is attached hereto.

Withdrawal of Objections

Specification

8. The objection to the disclosure because it contains an embedded hyperlink and/or other form of browser-executable code on p. 124, line 5 is withdrawn. The amendment to modify the hyperlink designation in the Response of 9/29/08 is acknowledged.

Claim Objections

9. The objection to Claim 28 is moot for the cancelled claim.

10. The objection to Claim 15 under 37 CFR 1.75(c), as being a duplicate claim of Claim 9 is moot for cancelled Claim 9.

Withdrawal of Rejections

Claim Rejections - 35 USC § 101

11. The rejection of Claims 1-6, 10-14, 16-18 and 28-33 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is moot for cancelled Claims 1, 2, 4, 5, 9-13, 17-18, 23, 28, 30 and 33 and withdrawn for the pending claims in view of the amendment to introduce the antibody being isolated.

Claim Rejections - 35 USC § 112, second paragraph

12. The rejection of Claims 17 and 18 for the recitation “has a high CDC activity” is moot for the cancelled claims.

13. The rejection of Claim 30 is moot for the cancelled claim.

Claim Rejections - 35 USC § 112, first paragraph

Enablement (designated “Enablement (2)” in the Office Action of 3/27/08)

14. The rejection of Claims 21-23 under 35 U.S.C. 112, first paragraph, is withdrawn. The rejection is moot for cancelled claim 23 and withdrawn for Claims 21 and 22 in view of the amendment to delete the "use" limitation for the claims 21 and 22 in the Response of 9/29/08.

Claim Rejections - 35 USC § 102

15. The rejection of Claims 9-18 and 33 under 35 U.S.C. 102(b) as being anticipated by Aburatani et al. (EP1411118; published 4/21/04; filed 6/21/02; cited in the IDS of 12/10/07) is moot for the cancelled claims and withdrawn for pending Claims 14-16 in view of the copy of the certified translation of the Japanese language priority document, JP 2004-2-3637, filed ***7/9/04***. The original rejection of Claims 14-16 under 102(b) is now new grounds for rejection under *102(a)* as set forth below.

16. The rejection of Claims 3, 7, 9-18 and 33 under 35 U.S.C. 102(e) as being anticipated by Aburatani et al. (WO/ 2004/022739; published 3/18/04; filed 9/4/02; cited in the IDS of 12/10/07; English language translation equivalent attached as EP 1541680; published 6/15/05; filed 4/9/03) is moot for the cancelled claims and withdrawn for pending Claims 14-16 in view of Applicants allegation on p. 24 of the Response of 9/29/08 that the reference is more properly a 102(a) art reference. The original rejection of Claims 14-16 under 102(e) is now new grounds for rejection under *102(a)* as set forth below.

Double Patenting

17. The provisional rejection of Claims 9 and 15 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of copending Application No. 11/414676 ("'676"; US 20060188510; filed 9/4/02) in view of Queen (USPN 5, 530,101; published June 25, 1996) is moot for the cancelled claim and withdrawn for Claim 15 in view of its new dependence on Claims 14 and 16.

Objections Maintained

Drawings

18. In addition to Replacement Sheets containing the corrected drawing figure(s) for Figures 1-20 filed on 9/29/08, applicant is required to submit a marked-up copy of each Replacement Sheet including annotations indicating the changes made to the previous version. The marked-up copy must be clearly labeled as "Annotated Sheets" and must be presented in the amendment or remarks section that explains the change(s) to the drawings. See 37 CFR 1.121(d)(1). Failure to timely submit the proposed drawing and marked-up copy will result in the abandonment of the application.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement (1)

19. The rejection of Claim 31 and new Claims 35, 40 and 42 under 35 U.S.C. 112, first paragraph, is maintained because the specification does not reasonably provide enablement for an anti-glypican 3 antibody comprising mixing any light chain or VL domain from a given parent anti-glypican 3 antibody with any heavy chain or VH domain from another anti-glypican 3 antibody; or any of the anti-glypican 3 antibodies (e.g., GC33, M11F1, M3B8, GC199, GC202, GC179, GC194(2), M13B3, L9G11, M6B1, M5B9, M10D2) comprising any amino acid substitution, deletion, addition and/or insertion.

The rejection was set forth in the Office Action of 3/27/08 as follows:

"Nature of the Invention/ Skill in the Art

The claims are interpreted as being drawn to an antibody comprising a VH region having the following CDRs: (1) VH CDRs SEQ ID NOS: 123, 124 and 125 (**GC33),** (2) VH CDRs SEQ ID NOS: 109, 110 and 111 (**M11F1)**, (3) VH CDRs SEQ ID NOS: 106, 107 and 108 **M3B8**, (4) VH CDRs SEQ ID NOS:132, 133 and 134 (**GC199),** (5) VH CDRs SEQ ID NOS:106, 135 and 136 (**GC202),** (6) VH CDRs SEQ ID NOS: 126, 127 and 128 (**GC179),** (7) VH CDRs SEQ ID NOS: 129, 130 and 131 (**GC194(1)**), (8) VH CDRs SEQ ID NOS: 103, 104 and 105 (**M13B3**), (9) VH CDRs SEQ ID NOS: 118, 121 and 122 (**L9G11**), (10) VH CDRs SEQ ID NOS: 115, 116 and 117 (**M6B1),** (11) VH CDRs SEQ ID NOS: 112, 113 and 114 (**M5B9**), and VH CDRs SEQ ID NOS: 118, 119 and 120 (**M10D2**) (Claim 1), or

an antibody comprising a VL region having the following CDRs: (1) VL CDRs SEQ ID NOS: 143, 144 and 158 (**GC33),** (2) VL CDRs SEQ ID NOS: 143, 144 and 145 (**M11F1)**, (3) VL CDRs SEQ ID NOS: 140, 141 and 142 (**M3B8)**, (4) VL CDRs SEQ ID NOS: 167, 168 and 169 (**GC199),** (5) VL CDRs SEQ ID NOS: 170, 144 and 171 (**GC202)**, (6) VL CDRs SEQ ID NOS: 159, 160 and 161 (**GC179),** (7) VL CDRs SEQ ID NOS: 162, 147, 163 **GC194(2)**, (8) VL CDRs SEQ ID NOS: 164, 165, 166 (**GC194(2)**), (9) VL CDRs SEQ ID NOS: 137, 138, 139 (**M13B3**), (10) VL CDRs SEQ ID NOS: 155, 156, 157 (**L9G11**), (11) VL CDRs SEQ ID NOS: 149, 150, 151 (**M6B1**), (12) VL CDRs SEQ ID NOS: 146, 147, 148 (**M5B9**), or (13) VL CDRs SEQ ID NOS: 152, 153, 154 (**M10D2**) (Claim 2), or

an antibody comprising a VH of SEQ ID NO: 84, 85, 86, 97, 88, 89 or 90 (Claim 4), or and antibody having a LV of SEQ ID NO: 92 (Claim 5), or a humanized antibody of Claims 1-6 (Claim 7), or an antibody having an activity equivalent to the antibody of Claim 7 having one or more amino acid substitutions, deletions, additions or insertions (claim 8), or a cell growth inhibitor comprising the antibody of Claim 7 (Claim 21), or an anti-cancer agent comprising the antibody of Claim 7 (Claim 22) for treating a hepatoma (Claim 23), or an antibody comprising a VL region having a CDR1 of SEQ ID NO: 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187 or 188, a CDR 2 of SEQ ID NO: 144 and a CDR3 of SEQ ID NO:158 (Claim 28), or an antibody comprising a VH region comprising CDR 1-3 of SEQ ID NOS: 123, 124 and 125, respectively, paired with a VL region comprising a CDR1 of SEQ ID NO: 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187 or 188, a CDR 2 of SEQ ID NO: 144 and a CDR3 of SEQ ID NO:158 (Claim 29), or an antibody comprising any VL region of SEQ ID NO: 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204 and 205 (Claim 31), or an antibody comprising any VL region of SEQ ID NO: 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204 and 205 paired with any VH region of SEQ ID NO: 84, 85, 86, 87, 88, 89 or 90 (Claim 31), or a human antibody of Claims 28-31 (Claim 32).

The relative skill in the art required to practice the invention is a molecular immunologist with a background in antibody biochemistry.

Disclosure in the Specification

The specification is enabling for producing hybridomas against glypican 3 protein and screening for the monoclonal anti-glypican 3 antibodies: **GC33** (VH CDRs SEQ ID NOS: 123, 124 and 125, and VL CDRs SEQ ID NOS: 143, 144 and 158); **M11F1** (VH CDRs SEQ ID NOS: 109, 110 and 111, and VL CDRs SEQ ID NOS: 143, 144 and 145); **M3B8** (VH CDRs SEQ ID NOS: 106, 107 and 108, and VL CDRs SEQ ID NOS: 140, 141 and 142); **GC199** (VH CDRs SEQ ID NOS:132, 133 and 134, and VL CDRs SEQ ID NOS: 167, 168 and 169); **GC202** (VH CDRs SEQ ID NOS:106, 135 and 136, and VL CDRs SEQ ID NOS: 170, 144 and 171); **GC179** (VH CDRs SEQ ID NOS: 126, 127 and 128, and VL CDRs SEQ ID NOS: 159, 160 and 161); **GC194(1)** (VH CDRs SEQ ID NOS: 129, 130 and 131, and VL CDRs SEQ ID NOS: 162, 147 and 163); **GC194(2)** (VH CDRs SEQ ID NOS: 129, 130 and 131, and VL CDRs SEQ ID NOS: 164, 165 and 166); **M13B3** (VH CDRs SEQ ID NOS: 103, 104 and 105, and VL CDRs SEQ ID NOS: 137, 138 and 139); **L9G11** (VH CDRs SEQ ID NOS: 118, 121 and 122, and VL CDRs SEQ ID NOS: 155, 156 and 157); **M6B1** (VH CDRs SEQ ID NOS: 115, 116 and 117, and VL CDRs SEQ ID NOS: 149, 150 and 151); **M5B9** (VH CDRs SEQ ID NOS: 112, 113 and 114, and VL CDRs SEQ ID NOS: 146, 147 and 148); and **M10D2** (VH CDRs SEQ ID NOS: 118, 119 and 120, and VL CDRs SEQ ID NOS: 152, 153 and 154) (Examples 6- 9, 13, 18); and

humanized versions of the GC33 monoclonal comprising a VH region of SEQ ID NO: 84, 85, 86, 87, 88, 89, or 90 paired with a VL of SEQ ID NO: 92 (Example 24); and

modified, humanized GC33 L chains comprising SEQ ID NO: 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204 or 205 paired with humanized, GC33 H chain of ver. k (SEQ ID NO:90) (Example 25).

The specification is not enabling for the antibodies encompassed by the scope of the claims including anti-glypican antibodies comprising a single VH or a single VL domain, or mixing VL CDRs from a given parent anti-glypican 3 antibody with another anti-glypican 3 antibody and/or mixing VH CDRs from a given parent anti-glypican 3 antibody with another anti-glypican 3 antibody; or mixing any light chain or VL domain from a given parent anti-glypican 3 antibody with any heavy chain or VH domain from another anti-glypican 3 antibody; or any of the anti-glypican 3 antibodies (e.g., GC33, M11F1, M3B8, GC199, GC202, GC179, GC194(2), M13B3, L9G11, M6B1, M5B9, M10D2) comprising any amino acid substitution, deletion, addition or insertion.

The claims are not commensurate in scope with the enablement provided in the specification. The specification does not support the broad scope of the claims which encompass modifications to the amino acid sequence of the antibody because the specification does not disclose the following:

The general tolerance to modification and extent of such tolerance;

The specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; and

The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed anti-glypican antibodies in manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions, or substitutions. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

Without such guidance, the changes which can be made in the antibodies structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).

Prior Art Status: Single Variable Domain Antibodies

Selecting and producing just any variable domain substituted antibody with the ability to properly associate and assemble into a fully functional antibody which maintains the binding specificity for the original antigen would be highly unpredictable based on the methods described in the specification and the prior art disclosures.

Smith-Gill et al. (J. Immunol. 139:4135-4144 (1987)) observed from chain recombination experiments that through interactions between the VH/VL pair, specificity for antigen is H chain determined, specific binding is increased when L chains of the same parental isotype are used, and that both H and L chains determine fine specificity.

Kumar et al. (J. Biol. Chem. 275:35129-35136 (2000)) discloses Fab molecules with anti-DNA (light chain) and anti-cardiolipin (heavy chain) binding activities, and that pairing of the partner chains is dependent on the particular H/L chain pairing.

Song et al. (Biochem Biophys Res Comm 268:390-394 (2000)) discloses that affinity and specificity of scFv for preS1 protein of HBV is dependent on S-S bond formation in conferring correct refolding of the fragments for retaining binding properties, and that L chains are predominant in antigen binding.

Prior Art Status: CDR-domain Modifications

The claims encompass antibodies comprising mixing CDR domains from different chains and possibly even different anti-glypican 3 antibodies. The claims encompass any amino acid substitution, deletion, addition and/or insertion to any region of the antibody. Applicants have not shown that any antibody comprising less than a full complement of VH CDR 1-3 and VL CDR 1-3 from a given parent anti-glypican 3 antibody would retain the antigen binding for glypican 3. In fact there are numerous publications acknowledging that the conformation of CDRs as well as framework regions (FR) influence binding.

MacCallum *et al.* (J. Mol. Biol. (1996) 262:732-745) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.).

Pascalis *et al.* (Journal of Immunology (2002) 169, 3076-3084) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left col.).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset *et al.* ((2003) BBRC 307, 198-205), which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset *et al.* also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and a framework residue located just before the H3 (see page 202, left col.).

Vajdos *et al.* ((2002) J. Mol. Biol. 320, 415-428) additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left col.).

Holm *et al* ((2007) Mol. Immunol. 44: 1075-1084) describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract).

Chen *et al.* (J. Mol. Bio. (1999) 293, 865-881) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866).

Wu *et al.* J. Mol. Biol. ((1999) 294, 151-162) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

Thus, while one can make the statement that a single CDR makes a significant contribution in the antigen binding, the residues in these CDRs are not the only residues that influence binding and in fact the prior art as well as applicants own disclosure do not support that it was clearly established, that the a single CDR domain alone is sufficient to define the binding specificity of an antibody, and that multiple antibodies can predictably be generated having the same binding specificity based on a single CDR (or less than full complement of VH and VL CDRs).

Analyzing applicants own disclosure, which while it does have divergent CDR residues, the majority of these heavy chain CDRs were paired with specific light chain CDRs. Additionally, the data seem to indicate that it is the frameworks and CDRs that contribute to antigen binding. Further, there are no working examples of mixing or matching of the light chain CDRs or heavy chain CDRs in just any framework and producing an anti-glypican 3 antibody that binds antigen as broadly claimed or suggested.

Prior Art Status: Conservative Amino Acid Substitutions within CDR/FR Residues

The claims encompass antibodies comprising VH domains, VL domains and CRDs comprising amino acid substitutions, deletions, additions and insertions. It is not well established in the art that all variable domains are amenable to any modifications much less even conservative modifications. Numerous publications acknowledge that even conservative substitutions would in fact change the binding ability of antibodies if not substantially reduce the affinity.

Brummell *et al.* (Biochemistry 32:1180-1187 (1993)) found that mutagenesis of the four HCDR3 contact residues for the carbohydrate antibody (Salmomella B O-polysaccharide) in no instance improved affinity but 60% of the mutants resulted in a 10-fold drop in binding constant (affinity electrophoresis value of 0.85), while still other mutants were lower (Table 1 and p. 1183, Col. 2, ¶2 to p. 1184, Col. 1, ¶1). Brummell demonstrates that no substitution retained antigen binding affinity similar to the wild type antibody despite targeted, conservative substitutions in known contact sites.

Kobayashi *et al.* (Protein Engineering 12:879-844 (1999)) discloses that a scFv for binding a DNA oligomer containing a (6-4) photoproduct with Phe or Tyr substitutions at Trp 33 retained "a large fraction of the wild-type binding affinity, while the Ala substitution diminished antigen binding" (Table 1). However, Kobayashi notes "replacing Trp 33 with Phe or Ala alters the local environment of the (6-4) photodimer since binding is accompanied by large fluorescence increases that are not seen with the wild-type scFv" (p. 883, Col. 2, ¶3).

Burks *et al.* (PNAS 94:412-417 (1997)) discloses scanning saturation mutagenesis of the anti-digoxin scFv (26-10) which also binds digitoxin and digoxigenin with high affinity and with 42-fold lower affinity to ouabain. 114 mutant scFvs were characterized for their affinities for digoxin, digitonin, digoxignenin and oubain. Histogram analysis of the mutants (Figure 2) reveals that "not all residues are optimized in even high affinity antibodies such as 26-10, and that the absence of close contact with the hapten confers higher plasticity, i.e., the ability to tolerate a wider range of substitutions without compromising binding (p. 415, Col. 2, ¶4- p. 416, ¶1).

Although Brummell *et al.*, Kobayashi *et al.* and Burks *et al.* introduced conservative amino acid substitutions into CDRs to examine binding effects these three references do not overcome the unpredictability in the art as far as demonstrating that any conservative substitution within any CDR can be made without affecting binding.

Jang *et al.* (Molec. Immunol. 35:1207-1217 (1998)) teach that single amino acid mutations to the CDRH3 of a scFV derived from 2C10, an anti-dsDNA autoantibody, reduced the binding activity about 20-50% compared to the unmutated scFv (Table 4).

Brorson *et al.* (J. Immunol. 163:6694-6701 (1999)) teach that single amino acid substitutions to the CDRs of IgM Abs for the bacterial protein, levan, are ablated.

Coleman (Research in Immunol. 145:33-36 (1994)) teaches that single amino acid changes within the interface of an antibody-antigen complex are important and that inasmuch as the interaction can tolerate amino acid sequence substitutions, "a very conservative substitution may abolish binding" while "in another, a non-conservative substitution may have very little effect on the binding" (p. 35, Col. 1, ¶1).

Unpredictability/Undue Experimentation

The specification provides no direction or guidance regarding how to produce the genus of antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Furthermore, while the level of skill required to generate the antibodies is that of a molecular biologist or molecular immunologist, the artisan of ordinary skill in the art would have been required to characterize the parent antibody, identify candidate amino acid residues for modifications in the FR and/or CDR domains, perform the mutagenesis on the FR and CDR domains, produce and express the modified antibodies, measure binding characteristics (e.g., binding specificity, equilibrium dissociation constant (K_D), dissociation and association rates (K_{off} and K_{on} respectively), and binding affinity and/or avidity compared with the parent antibody) in a BIAcore assay, and

then finally perform bioassays to identify any one or more of the characteristics of an antibody. The technology to perform these experiments was available at the time of application filing, but the amount of experimentation required to generate even a single FR- and/or CDR-modified antibody meeting all of the claim limitations would not have been routine much less could one of ordinary skill in the art predict that any one or combination of all the FR and CDR modifications encompassed by the claims would result in *just any* antibody clone having retained the antigen binding activity (MPEP 2164.06, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (In re Wands, 858 F.2d 731, 737, 8 USQP2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976))."

Applicants' allegations spanning pp. 17-22 of the Response of 9/29/08 have been considered and are not found persuasive. Applicants' allege in summary "The available art at the time of filing of the application acknowledged that many single- amino-acid-residue changes can be made in the CDRs and FRs of antibodies without significantly affecting binding activity."

Response to Arguments

The pending rejected claims still read on an anti-glypican 3 antibody comprising mixing any light chain or VL domain from a given parent anti-glypican 3 antibody with any heavy chain or VH domain from another anti-glypican 3 antibody; or any of the anti-glypican 3 antibodies (e.g., GC33, M11F1, M3B8, GC199, GC202, GC179, GC194(2), M13B3, L9G11, M6B1, M5B9, M10D2) comprising any amino acid substitution, deletion, addition and/or insertion. Applicants have not addressed that it is predictable for the ordinary artisan to obtain a functional working antibody comprising the modifications encompassed by the claims.

For example, Dufner (Trends Biotechnol. 24(11):523-29 (2006)) teaches: "specific structural information - on the antibody to be optimized, its antigen and their interaction- is rarely available or lacks the high resolution required to determine accurately important details such as side-chain conformations, hydrogen-bonding

patterns and the position of water molecules" (p. 527, Col. 2, ¶1). Applicants specification and the evidence of record does not define specific structural information detailing the number of and exact position of hotspots in the CDRs which "can vary considerably from case to case and therefore cannot be predicted" (legend to Figure 2 of Dufner). Thus even with the availability of screening approaches as taught in the specification and Dufner, the ordinary artisan could not predict the hotspots much less those residues critical for conferring specific antigen binding for any of the claimed CDRs and FRs absent further additional information and experimentation. What does a sequence alignment for the CDRs and/or FRs look like for a "reasonable" number of glypican 3 antibodies that would guide the ordinary artisan in determining the important common shared or similar binding residues that confer specific antigen binding? Are any hotspots present in the CDRs (and/or FRs), what is the frequency of those hot spots and what are the positions of those hot spots? Numerous questions remain that point to the lack of predictability for the scope of the instant claimed antibodies.

For these reasons, the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. The rejection of Claims 14, 16 and (new Claims 36 and 38) under 35 U.S.C. 102(b) as being anticipated by Gonzalez et al. (J. Cell Biol. 141:1407-1414 (1998); cited in the IDS of 12/10/07) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 3/27/08 as follows:

"Gonzalez discloses generating sheep polyclonal antibodies against a human GPC3 fragment containing the last 70 amino acids (i.e., residues 511-580) (M & M, p. 1408, Col. 2, ¶ 7). A polyclonal antibody of Gonzalez could reasonably be expected to bind any epitope falling within the structure of the 70 amino acid residues of the C-terminal fragment of GPC3. Thus it is generally expected that within a heterogeneous population of polyclonal antibodies, some could be found that would bind to a peptide consisting of residues 524-563 or residues 537-563 or residues 550-563 or residues 544 or residues 546-551 of GPC3 or that there would be an antibody which does not bind to a peptide consisting of residues 550-563 of glypican 3. Further within the heterogeneous population of polyclonal antibodies, some could be found that could bind the same epitope as the GC33 antibody or an antibody comprising the CDRs of GC33. One would readily envisage that the antibody of Gonzalez has the same properties of binding GPC3. "The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property, which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1997)."

Applicants allege on p. 23 of the Response of 9/29/08 "Gonzalez et al. does not teach or suggest the isolated antibodies as recited in amended claims 14 and 16;...."

Response to Arguments

In order for Gonzalez to characterize the antibodies in vitro, it is necessary that they are isolated from the sheep. Thus the claimed antibody appears to be the same as the prior art antibodies, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re

Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

21. The rejection of Claims 14, 16 and (new Claims 36 and 38) under 35 U.S.C. 102(b) as being anticipated by Pilia et al. (Nature Genetics 12:241-247 (1996); cited in the IDS of 12/10/07) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 3/27/08 as follows:

"Pilia discloses producing rabbit polyclonal antibodies generated against 4 peptide sequences described as having "marked hydrophobic character" and one of which corresponds to residues 533-547 of human GPC3, specifically, DDAPGNSQQATPKDN (p. 247, Col. 1, ¶3). The peptide of Pilia is overlapping in whole or in part with the peptides of Claims 10-14 and 33. It is generally expected that within a heterogeneous population of polyclonal antibodies, some could be found that would bind to a peptide consisting of residues 524-563 or residues 537-563 or residues 550-563 or residues 544 or residues 546-551 of GPC3 or that there would be an antibody which does not bind to a peptide consisting of residues 550-563 of glypican 3. Further within the heterogeneous population of polyclonal antibodies, some could be found that could bind the same epitope as the GC33 antibody or an antibody comprising the CDRs of GC33. One would readily envisage that the antibodies of Pilia could have the same properties of binding GPC3. "The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property, which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1997)."

Applicants allege on pp. 23-24 of the Response of 9/29/08 "Pilia et al. does not teach or suggest the isolated antibodies as recited in amended claims 14 and 16;...."

Response to Arguments

In order for Pilia to characterize the antibodies in vitro, it is necessary that they are isolated from the rabbit. Thus the claimed antibody appears to be the same as the prior art antibodies, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural

and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

22. The provisional rejection of Claims 14 and 15 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9 and 23-29 of copending Application No. 10/526,741 ("'741"; US 20060167232; filed 9/4/02; cited in the IDS of 12/10/07) is maintained.

Applicants request to hold the rejection in abeyance until further disposition of the claims is acknowledged on p. 25 of the Response of 9/29/08, however, their response is incomplete and the rejection is maintained.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

23. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claim 8 is indefinite for the recitation "wherein one amino acid residue substituted, deleted, added, or inserted among the heavy chain CDRs and light chain CDRs taken together" because the phrase appears to be incomplete. What happens when the recited amino acids modifications are taken together? The ordinary artisan could not determine the metes and bounds of this claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

24. Claims 14-16, 32, 34, 36-38 and 41 are rejected under 35 U.S.C. 102(a) as being anticipated by Aburatani et al. (EP1411118; published 4/21/04; filed 6/21/02; cited in the IDS of 12/10/07).

Claim 14 is interpreted as being drawn to an isolated antibody capable of binding a peptide consisting of residues 546-551 of glypican 3 (Claim 14),

Claim 16 is interpreted as being drawn to an antibody that binds an epitope to which a second antibody comprising the VH CDR1-3 of SEQ ID NO: 123, 124 and 125, respectively, and the VL CDR1-3 of SEQ ID NO: 143, 144 and 158, respectively. The "second antibody" comprises the CDRs from the GC33 Mab, which as disclosed in the specification binds to an epitope in the C-terminus of GPC3.

Claim 15 is interpreted as being drawn to the antibody of Claim 14 or 16 where the antibody is humanized.

Claim 32 is interpreted as being drawn on a human antibody for the antibodies of Claims14 and 16.

Claim 34 is interpreted as being drawn to the antibody of Claim 14 which binds a peptide separated gel filtration and Western blotting.

Claims 36-38 and 41 are interpreted as being drawn to a composition comprising the antibody of Claims 14-16 and 32, respectively.

Aburatani discloses glypican 3 (GPC3) antibodies including polyclonal, monoclonal [0015] or recombinant antibodies such as chimeric or humanized antibodies [0041-0047] generated against human GPC3 or a peptide thereof [0018]. The antibodies of Aburatani are necessarily isolated in order for the antibodies to be

characterized in vitro. A polyclonal or monoclonal antibody of Aburatani could reasonably be expected to bind any epitope falling within the structure of human GPC3 including the C-terminus. Aburatani discloses methods for detecting the antibodies and pharmaceutical compositions comprising the antibodies. Thus it is generally expected that within a heterogeneous population of polyclonal antibodies, some could be found that would bind to a peptide consisting of residues 546-551 of GPC3. Further within the heterogeneous population of polyclonal antibodies, some could be found that could bind the same epitope as the GC33 antibody or an antibody comprising the CDRs of GC33. One would readily envisage that the antibody of Aburatani has the same properties of binding GPC3 and that humanized forms could be made therefrom. "The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property, which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1997).

25. Claims 14-16, 32, 34, 36-38 and 41 are rejected under 35 U.S.C. 102(a) as being anticipated by Aburatani et al. (WO 2004/022739; published 3/18/04; filed 9/4/02; cited in the IDS of 12/10/07; English language translation equivalent attached as EP 1541680; published 6/15/05; filed 4/9/03).

The interpretation of Claims 14-16, 32, 34, 36-38 and 41 is discussed above under section 24.

Aburatani discloses generating polyclonal or monoclonal antibodies (or humanized forms of these antibodies [0066-0070]) capable of binding C-terminal fragments to glypican 3, for example [0035-0038]. All of these anribodies are necessarily isolated in order for Aburatani to determine there binding properties in vitro. It is generally expected that within a heterogeneous population of polyclonal antibodies, and even amongst a pool of monoclonal antibodies, that some could be found that would bind to a peptide consisting of residues 524-563 or residues 537-563 or residues 550-563 or residues 544 or residues 546-551 of GPC3 or that there would be an antibody which does not bind to a peptide consisting of residues 550-563 of glypican 3. Further within the heterogeneous population of polyclonal antibodies, some could be found that could bind the same epitope as the GC33 antibody or an antibody comprising the CDRs of GC33. One would readily envisage that the antibodies of Aburatani could have the same properties of binding GPC3. “The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.” Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property, which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1997).

Conclusion

26. Claims 3, 6, 7, 21, 22, 29 and 39 are in condition for allowance. The claims are directed to the anti-glypican 3 antibody designated GC33 and VH and VL domain variants thereof. The GC33 antibody and VH/VL variants thereof are free of prior art.

27. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Partial Signatory Authority